Successful Use of Venovenous Extracorporeal Membrane Oxygenation for Complicated H1N1 Pneumonia Refractory to Mechanical Ventilation

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Abstract: In April 2009, novel H1N1 influenza A pneumonia was initially identified in young adults by the Mexican Health Ministry. Previously healthy patients progressing to multisystem organ failure were common. Worldwide, hospitals reported surges in intensive care admissions during the initial phase of the pandemic. In patients with H1N1 pneumonia refractory to mechanical ventilation, centers were initially reporting low survival rates despite the use of extracorporeal membrane oxygenation (ECMO). The initial poor outcomes and protracted ECMO treatment epochs resulted in centers limiting or withholding the use of ECMO in this population. With respect to children with H1N1 infection there was uncertainty concerning optimal incorporation of ECMO as a therapeutic option. In children with rapidly progressive pneumonia and hypoxia refractory to mechanical ventilation, venovenous (VV) ECMO has been successfully used with survival ranging from 40–60% depending on the etiology. We report the successful use of VV ECMO in two children with confirmed novel H1N1 complicated by bacterial pneumonia or morbid obesity. Prompt initiation of VV ECMO resulted in rapid clinical improvement, radiographic resolution of diffuse consolidation, and return of full neurocognitive function. For children with rapidly progressive respiratory distress on conventional ventilation, VV ECMO can be used to improve outcomes when initiated early in the disease process even in children with a significant co-morbidity.

Keywords: extracorporeal membrane oxygenation, H1N1, influenza, methicillin-resistant staphylococcus aureus, acute respiratory distress, hypoxia.

The severity of novel influenza A virus subtype H1N1 in young adults was initially described by the Mexican Health Ministry in April 2009 (1). The number of previously healthy patients progressing to respiratory and multisystem organ failure was common (2,3). Worldwide, hospitals reported surges in intensive care admissions during the initial phase of the pandemic (4–6). In Canada, 17% of all hospitalized patients were admitted to the intensive care unit and suffered a mortality rate approaching 5% (6). In patients with H1N1 pneumonia refractory to mechanical ventilation, some centers were reporting low survival rates despite the use of extracorporeal membrane oxygenation (ECMO). The initial poor outcomes and protracted ECMO treatment epochs resulted in centers limiting or withholding the use of ECMO in this population. With respect to children with H1N1 infection there was also uncertainty concerning optimal incorporation of ECMO as a therapeutic option. Previously, in children with rapidly progressive pneumonia and hypoxia refractory to mechanical ventilation, venovenous (VV) ECMO has been successfully used with survival ranging from 40–60% depending on the etiology (7). We report the successful use of VV ECMO in two children with confirmed novel H1N1 complicated by bacterial pneumonia or morbid obesity.

CLINICAL PRESENTATIONS

Case One

A 7-year-old, 23 kg, 127 cm, previously healthy female presented to the emergency department with a 2-day history of fever, emesis, and fatigue. Prior to presentation, she had not been vaccinated for influenza. Initial vital signs (VS) were temperature 39.3°C, heart rate 158 bpm, blood pressure 88/42/58 mmHg, respiratory rate 32 breaths/min, and peripheral oxygen (O₂) saturation 80%. Clinical assessment revealed absent breaths on the right and muted
breath sounds over the left chest. Pulses were weak and capillary refill was delayed. Supplemental $O_2$ at 15 L/min was delivered by non-rebreather mask raising $O_2$ saturation above 95%. Laboratory analysis revealed white cell count 2600 cells/mm$^3$, neutrophils 43%, band forms 17%, and lymphocytes 34%. Chest radiography showed near complete consolidation of the right lung and hilar opacification of the left lung. Initial management included two 20 mL/kg normal saline infusions, intravenous vancomycin, and ceftriaxone.

In the pediatric intensive care unit, work of breathing increased dramatically and $O_2$ saturation fell rapidly to 83%. The initial arterial blood gas measurements showed pH 7.25, $CO_2$ 74 mmHg, and $PaO_2$ 51 mmHg. She was orally intubated for hypoxic respiratory failure. Conventional mechanical ventilation (CMV) was attempted for 6 hours but $O_2$ saturation proved difficult to maintain above 85% despite positive end-expiratory pressure (PEEP) reaching 14 cm H$_2$O, $FiO_2$ 1.0, plateau pressure 34 cm H$_2$O, and mean airway pressure 20 cm H$_2$O. Oxygenation index (OI) ranged from 32–35. A repeat chest radiograph revealed worsening consolidation in the right lung and increased opacification in the left lung. Within 1 hour of initiation of CMV, hemodynamic instability ensued marked by hypotension (BP systolic range 62–68 mmHg), worsening tachycardia (HR range 170–178 bpm), diminished peripheral pulses, and delayed peripheral capillary refill (>5 seconds) and urine output (<0.25 mL/kg/h). Serum lactate level rose from an admission value of 1.8 mmol/L to 5.5 mmol/L. Hemodynamic values improved with a combination of dopamine, epinephrine, vasopressin, normal saline, and 5% albumin volume infusions totaling 90 mL/kg. Serum lactate levels continued to rise to 7.2 mmol/L indicating worsening tissue perfusion. Bronchoscopy with bronchoalveolar lavage (BAL) confirmed inflamed airways with neutrophils and gram-positive cocci. Methicillin resistant *Staphylococcus aureus* (MRSA) and influenza A grew from cultures of the BAL fluid. The Influenza A H1N1 strain was confirmed by the Nebraska State Health Reference Laboratory. Due to the inability to maintain adequate gas exchange by CMV, insufficient of tissue perfusion based on persistent signs of delayed capillary refill (>4 sec), and worsening lactic acidosis, the child was placed on VV ECMO. Ventilator support was reduced to delivered rate 10 breaths/min, PEEP 10 cm H$_2$O, and peak inspiratory pressure (PIP) 20 cm H$_2$O.

Following initiation of VV ECMO, catecholamine and vasopressin infusions were quickly weaned and eliminated within 8 hours. Hemodynamic values and tissue perfusion improved as evidenced by a rise in blood pressure to systolic range of 88–98 mmHg, heart rate fall to 136–144 bpm, improved capillary refill (<3 seconds), improved pulse strength, and serum lactate levels falling to <2 mmol/L. Oseltamivir (Genentech, San Francisco, CA) was administered enterally. Dosing was based on patient weight at 2 mg/kg/dose given twice daily for 5 days. Gas exchange was easily maintained on ECMO circuit flow rate of 100 mL/kg. By day 5 of the ECMO run, significant reductions in opacification were noted in both lungs. Pulmonary compliance improved as evidenced by a rise in mechanical tidal volume from 1.8 mL/kg to 5.1 mL/kg on a PIP of 20 cm H$_2$O. Near complete radiographic resolution of pulmonary opacities was evident by day 7. Successful separation from VV ECMO occurred on day 7 followed by extubation the next day. Ceftriaxone was discontinued after 48 hours and vancomycin was continued to complete a 14-day course. Following a further 10-day course of physical rehabilitation, the child was discharged home having returned to her pre-illness respiratory, physical, and cognitive baseline.

**Case Two**

A 19-year-old morbidly obese male with Prader-Willi syndrome was admitted following several days of fever, headache, and fatigue to treat bronchopneumonia unresponsive to oral azithromycin. He had not received influenza vaccination. Physical parameters were height 170 cm, weight 109 kg, and body mass index 37. Initial VS were temperature 38.4°C, heart rate 132 bpm, blood pressure 149/89/108 mmHg, respiratory rate 45 breaths/minute, and peripheral $O_2$ saturation 70%. Examination revealed crackles in the right lower chest. Initial management included 15 L/min high flow $O_2$ via non-rebreather mask to achieve 94% peripheral $O_2$ saturation, and intravenous ceftriaxone. Lab studies revealed white blood cell count was 3600 cells/mm$^3$, neutrophils 73%, no band forms, and 21% lymphocytes. Chest radiograph showed irregular areas of opacification in both lung fields. Eight hours after admission to the general inpatient unit, he was transferred to the pediatric intensive care unit due to excessive work of breathing and increasing oxygen requirements. Within 36 hours of hospital admission he failed to maintain $O_2$ saturation greater than 85% despite multiple measures including high flow $O_2$ to 15 L/min by non-rebreather mask, noninvasive bi-level positive airway pressure, and CMV. Because of worsening respiratory acidosis and refractory hypoxia (pH 7.10, $PCO_2$ 86 mmHg, $PaO_2$ 62 mmHg), he was converted to high frequency oscillatory ventilation. Despite high frequency oscillatory ventilation (maximum settings 3 Hz, MAP 40 mmHg, $ΔP$ 58 mmHg), he failed to maintain adequate oxygenation and ventilation. After 7 hours, oxygenation failed to improve (OI ranged from 27–31) and the patient was ultimately placed on VV-ECMO, 51 hours after admission. Wash specimens obtained by BAL were negative for bacteria, tuberculosis, and fungus. Influenza A was cultured from the nasopharynx and confirmed to be the H1N1 strain by the Nebraska State Health Reference Laboratory. A 5-day course of oseltamivir 75/mg/dose was given enterally twice daily based on published adult dosing recommendations. Support from VV ECMO was discontinued after 9 days and the total mechanical ventilation period

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was 21 days. The child fully recovered within 6 weeks to his pre-illness respiratory, physical, and cognitive baseline.

ECMO EQUIPMENT AND CONDUCT

For our first patient, VV ECMO was instituted with an 18 Fr Edwards Venous cannula (Edwards Lifesciences, Irvine, CA) in the left femoral vein and a 14 Fr Edwards arterial cannula in the right internal jugular vein. We were able to flow 70–80 mL/kg/min and able to bring our SaO₂ above 80% for the remainder of the ECMO run. For our second patient, we used a 27 Fr Avalon VV ECMO Cannula (Avalon Laboratories, Rancho Dominguez, CA) inserted into the right internal jugular vein and were able to sustain 80 mL/kg/min flows or better for the entire ECMO run. Both patients were placed on a Sorin SIII Roller Pump System (Sorin, Milan, Italy) with positive and negative servo controlled shut offs with the positive being 300 mmHg and the negative being −50 mmHg as the shut off. For the first patient a 3/8” venous and 1/4” arterial and a 3/8” ECMO Tygon boot were used for the tubing system with X-Coating (Terumo Cardiovascular, Ann Arbor, MI). For the second patient a 3/8” arterial and venous and 1/2” ECMO Tygon boot were used, again with X-Coating by Terumo. A Terumo CDI 500 was used for both patients giving us both arterial blood gas as well as venous saturation and hematocrit. The device was calibrated every 8 hours of the ECMO run. A Jostra QuadroxD oxygenator with Safeline coating (Maquet, Rastatt, Germany) was used with both ECMO runs and the FiO₂ was maintained at 100% on the ECMO circuit for both patients for the entire run until the lungs started to recover and the peripheral SaO₂ was above 90%. The FiO₂ on the ECMO circuit was then weaned to keep the SaO₂ above 90%. Both patients received continuous arterial-venous hemodialysis using the Terumo HCOSSS hemofilter and were run at 300 mL/min on the dialysate inflow and 300 mL/min plus hourly fluid intake as the dialysate outflow for the entire ECMO run. Activated clotting times were maintained at a level of 160–200 seconds and heparin was titrated from 25 U/kg/hr to 50 U/kg/hr to maintain this level. Anti-thrombin three (ATIII) levels were measured every 12 hours and recombinant ATIII was given to maintain an ATIII level above 60%.

DISCUSSION

The recent novel H1N1 pandemic demonstrated the rapidly progressive nature of this disease. Centers worldwide reported acute hypoxic respiratory failure unresponsive to conventional mechanical ventilation. Our cases not only illustrate the severity of disease, but also the potential for successful outcome when ECMO is used early in the clinical course.

As of July 2010, the global H1N1 Extracorporeal Life Support Organization (ELSO) registry reported a total of 20 pediatric cases aged 5–10-years-old with 11 survivors and 17 cases with nine survivors aged 15–20-years-old (8). Our single institution experience represents 10% of reported survivors in the pediatric population.

Our decision to provide extracorporeal support for children with severe respiratory failure secondary to H1N1 pneumonia predated the arrival of our patients by 6 months. As part of our preparation for a possible local H1N1 outbreak with large numbers of children suffering respiratory failure as a result, our institution analyzed in detail the initial reports from the Australian experience with H1N1 pneumonia (5). One of our feared shortfalls was the ability to provide extracorporeal support for a dramatically increased number of patients. Therefore, we focused on training additional bedside ECMO specialists, upgrading and expanding current equipment, and ensuring adequate nursing and bed space resources.

Our institution is one of the regions’ busiest cardiac centers, which traditionally provides almost exclusively venoarterial (VA) ECMO. Avoidance of arterial cannulation provides distinct advantages including decreased rates of catastrophic embolic events and avoidance of damage to the arterial vessel system by the large bore arterial cannula as well as avoidance of multiple cannulation sites (9,10). Given the ages of our patients, preferential arterial cannulation for VA ECMO would have required utilizing the femoral artery. This unfortunately creates a situation whereby the ECMO circulation is directly competing with intrinsic cardiac output. For patients with uncompromised intrinsic cardiac function such as our two cases, the cerebral and coronary blood would be supplied by poorly oxygenated blood exiting the heart. Both of our patients were supported with VV ECMO. In cases of acute-severe-respiratory disease with otherwise normal cardiac function, success with this mode is well supported, and improved survival compared to VA ECMO has been demonstrated (11,12). Although VV ECMO obviates some risks imposed by arterial cannulation, the risk of extracorporeal support remains considerable including pump failure, tubing rupture, hemolysis, thromboembolism, sepsis, and various bleeding complications ranging in severity from mild to life-threatening.

The major disadvantage of VV ECMO is that it does not directly support cardiac function. Maintenance of systemic perfusion and oxygenation therefore is directly dependent on adequate intrinsic cardiac function. Case one represented a difficult decision because the child was receiving multiple high-dose vasoactive drugs for blood pressure support possibly indicating significant myocardial depression. However, it was our belief that the patient’s ventilator support could diminish significantly once ECMO was initiated. This would result in a significant reduction in delivered air
pressure. The concomitant reduction in intrathoracic pressure would lead to improved thoracic venous return and improved cardiac output. Our conjecture appeared to be correct since the first child was quickly weaned from inotropic and vasopressor support while hemodynamic indices and tissue perfusion improved. If hemodynamic instability had worsened, conversion to VA ECMO was planned as an alternative option, which would have provided sufficient cardiac support.

Our experience was also marked by the limited duration of total cannulation time. Both patients were decannulated after 7 and 9 days respectively, shorter than previous reports (4,5). Several factors may have contributed to our observation, the most important being early recognition of the pulmonary disease process that appeared refractory to mechanical ventilation, but had a reasonable chance of survival if extracorporeal support of gas exchange and lung rest was instituted. Determination of the appropriate time frame in which ECMO would confer a survival advantage compared to conventional ventilator support continues to be debated, but increasing evidence appears to support early introduction. Pranikoff et al. (13) determined in a population of 36 patients treated with extracorporeal support for respiratory failure refractory to mechanical ventilation a nine fold higher risk of death in patients treated for ≥5 days compared to patients placed on mechanical ventilation for <5 days. The attributed cause for the discrepancy in mortality between the two groups was ventilator associated lung injury. During the influenza pandemic in the summer of 2009, the published New Zealand/Australian experience used ECMO to treat 68 patients with influenza A infection, 89% confirmed as novel H1N1 strain (5). All patients were placed on ECMO within 1–5 days of developing respiratory failure. Mean ECMO duration was 10 days (range 7–14 days). The mortality rate in this population was 21%. These results compare favorably to recently published series involving the use of ECMO for hypoxemic respiratory failure due to a wide variety of causes where mortality ranged from 37–50% (13,14). Additional data from the ELSO registry has also catalogued that patients with respiratory disease caused by the novel H1N1 strain of influenza identified a survival rate of 75% when subjects were transitioned to ECMO prior to reaching 7 days of mechanical ventilation compared to 30% survival when mechanical ventilation duration was longer than 7 days (8).

Currently there is no firm clinical, radiographic, or laboratory criteria to trigger the referral for or initiation of extracorporeal support for severe respiratory failure. Our clinical practice is to strongly consider initiation of ECMO when OI reaches 25–30 from hypoxemic respiratory failure due to a potentially reversible disease process that does not respond to mechanical ventilation within 12–24 hours or if significant cardiac dysfunction and tissue oxygenation does not improve significantly with inotropic support and fluid challenges. Our preferred choice is VV ECMO for respiratory failure in which cardiac function, tissue perfusion, and oxygenation appears adequate. If cardiac dysfunction ensues, conversion to VA ECMO is performed.

Almost all centers offering extracorporeal support have established general guidelines concerning thresholds for the initiation of ECMO that are largely based on the institutional consensus. The recent experience of Australia and New Zealand Extracorporeal Membrane Oxygenation study (5) was published after our two cases and the total patient population (n = 68) manifested a median Murray lung injury score of 3.8, blood pH of 7.20, PCO₂ 69 mmHg, and lowest PaO₂/FiO₂ ratio of 56 while on mechanical ventilator settings of median highest PEEP of 18 cm H₂O, PIP 36 cm H₂O, and FiO₂ 1.0. For this specific disease process, these values in some combination could potentially serve as clinical triggers for initiating ECMO. However, until broad international consensus is established, individual institutional guidelines could be adopted for initiating extracorporeal support in patients with influenza induced lung injury.

Our experience is to some degree surprising since both patients had risk factors that could contribute to higher morbidity and mortality. In the first case, MRSA co-infection was thought to be a significant contributor to the pneumonic process. In the second case, morbid obesity was a preexisting condition. For seasonal influenza A and novel H1N1 infection, known risk factors for death and prolonged hospitalization include lack of seasonal influenza vaccination, some ethnic groups, pregnancy, immunocompromised, presence of chronic conditions, and co-infection with MRSA or Streptococcus pneumoniae (6,15–20).

Co-morbid conditions and their effect of survival in patients with influenza pneumonia treated with ECMO have not been reported. Our limited experience delineates a potential favorable role for ECMO in reducing morbidity and mortality in children with co-morbid conditions suffering from influenza pneumonia.

The use of standard dose oseltamivir in both seasonal and pandemic H1N1 influenza is supported in some populations (21,22). For children under a weight based dose of 2 mg/kg/dose given twice daily for 5 days is recommended. In adults, 75 mg/kg/dose given twice daily is standard therapy. In both cases, enteral administration was the only option for drug administration. An intravenous preparation is currently under investigation in critically ill patients. The beneficial effect of antiviral treatment with neuraminidase inhibitors, against influenza pneumonia and respiratory failure in children, remains to be determined. Moreover, serum oseltamivir levels in critically ill pediatric patients, as well as those with increased circulating blood volume when on ECMO, have not been reported.
CONCLUSION

We report here the successful use of VV ECMO in the setting of rapidly progressive novel H1N1 influenza in two children complicated by either a co-morbid condition or bacterial co-infection. Anticipation of emerging pandemics is vital in preparing an institution for increased resource demand. Based on the cumulative experience of the member institutions from the ELSO registry, children with H1N1 influenza infection refractory to mechanical ventilation can achieve functionally intact survival using ECMO. Although the overall numbers are small, survival rates appear to be equal to those witnessed with other forms of viral and bacterial pneumonia. The use of VV ECMO should be considered as a viable option in lieu of VA ECMO if hemodynamic compromise is not severe.

REFERENCES